HEARTFAID

D5 – Medical-clinical processes and requirements in HF domain and formulation of the decision making problems

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HEARTFAID

A KNOWLEDGE BASED PLATFORM OF SERVICES FOR SUPPORTING MEDICAL-CLINICAL MANAGEMENT OF THE HEART FAILURE WITHIN THE ELDERLY POPULATION

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Consortium

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- FORTHNET S. A.- Hellenic Telecommunications and Telematic Applications Company S. A. (Greece)
- SYNAP- Synapsis s.r.l. (Italy)
- CNR- Consiglio Nazionale delle Ricerche (Italy)
- FORTH-Foundation for Research and Technology Hellas (Greece)
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D5 – Medical-clinical processes and requirements in HF domain and formulation of the decision making problems

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Short description
The aim of this document is to describe, in a complete and systematic way, the main processes related to the management of heart failure patients. Moreover, section 8 collects the descriptions of the most relevant decisional problems in this field.

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1.0	first draft of the document	06/04/2006
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Executive Summary

The deliverable number five, "Medical – clinical processes and requirements in HF domain. Relevance to formulation of the decision making problems", collects the results of the tasks T1.1 and T1.2 of the Work Package WP1. The partners involved in preparing the document have been UNICAL, UNICZ, JUMC, UNIMIB and AUXOL.

This document describes the clinical State of Art of the Heart Failure (HF) field. The authors aimed at giving a complete and detailed description of the whole medical knowledge related to heart failure syndrome, with a particular attention to the definition of diagnostic and care processes.

Starting from a deep analysis of the medical and clinical procedures of the relevant domain, from the study of the guidelines and protocols for the evaluation and clinical management of HF patients, and from the relevant results of the evidence based medicine in HF domain, the authors have identified, formulated and assessed the most important information relevant to the HF domain.

Moreover the description of the medical knowledge has been structured in a very schematic way, in order to facilitate its readability and understanding by non clinical readers.

In its final part the document lists the principal decision making problems that clinicians face during the treatment of Heart Failure patients. The aforementioned list of problems statements will be a precious support in order to define the structure and the services of HEARTFAID platform.

The document structure is subdivided into several parts, in order to ensure an easy information retrieval and a logical separation of the contents:

1) Heart Failure Description (Chapters 1 – 4):
   The aim of the first part is to give an introductory and general description of Heart Failure syndrome, with particular regard to pathophysiology and epidemiological issues.

2) Heart Failure Diagnosis process (Chapter 5):
   In this chapter the procedures related to the diagnostic evaluation of Heart Failure patients have been described. First a general diagnostic process has been presented, and then it has been detailed throughout the chapter. In particular, for each diagnostic examination a schematic description has been reported, with the list of conditions needed for the perform the exam, the data that the exam can give and the information that physicians can deduce.

3) Heart Failure Prognosis (Chapter 6):
   The prognostic evaluation of heart failure patient is a very difficult activity, due at the lack of large and randomized studies in this field and to the many confounders affecting the prognostic evaluation. The chapter 6 presents and outlines the information known by the medical community.

4) Heart Failure treatment processes (Chapter 7):
   Several treatments are available in order to treat heart failure symptoms and causes. In the 7th chapter different approaches are presented, especially pharmacological treatments. For each drug used in the Heart Failure field a schema has been defined. These algorithms, analogous to the schemas used for the Diagnostic process, collect the following information:
   1. condition for the use of the drug;
   2. titration methodologies;
   3. contraindications;
   4. which parameters should be monitored in order to manage the follow up

5) Formulation of decision making problems (Chapter 8):
   This chapter collects the results of the Task T1.2. The main decisional problems relevant for the treatment of Heart Failure patients are listed. In particular the partners focussed on the early identification of the symptoms of decompensation of Heart failure patients. This should be of great help in order to prevent the worsening of the patient status. In this way it should be possible to optimize the therapy and to reduce hospitalization costs.

6) Annexes
   The annexes of the document collect the lists of parameters that are important for the diagnostic and prognostic evaluation and for the follow up of Heart Failure patient. These lists will be useful for the project continuation, especially for the definition and implementation of data warehouse and data collection system.

1 Descriptive Terms of Heart Failure

1.1 Definition of chronic heart failure

None definition is entirely satisfactory and one commonly used definition is: heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. The diagnosis of heart failure relies on clinical judgement based on a history, physical examination and appropriate investigations. The Task Force considers the essential components of heart failure to be a syndrome where the patients should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest.

1.2 Acute vs chronic heart failure

Chronic heart failure, often punctuated by acute exacerbations, is the most common form of heart failure. The term acute heart failure is often used, exclusively, to mean acute (cardiogenic) dyspnoea characterized by signs of pulmonary congestion including pulmonary oedema. However, acute heart failure could also apply to cardiogenic shock, a syndrome characterized by a low arterial pressure, oliguria and a cool periphery.

1.3 Systolic vs diastolic heart failure

Usually, heart failure is associated with evidence of left ventricular systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. Diastolic heart failure is often presumed to be present when symptoms and signs of heart failure occur in the presence of a preserved left ventricular systolic function (normal ejection fraction/normal end-diastolic volume) at rest.

1.4 Other descriptive terms in heart failure

Right and left heart failure refer to syndromes presenting predominantly with congestion of the systemic or pulmonary veins, respectively. High and low-output, forward and backward, overt, treated, congestive and undulating are other descriptive terms still in occasional use; the clinical utility of these terms has yet to be determined. Mild, moderate or severe heart failure is used as a clinical symptomatic description where mild is used for patients who can move around with no important limitations (NYHA I) , severe for patients who are markedly symptomatic and need frequent medical attention (NYHA IV) and moderate for the remaining patient cohort (NYHA II-III).

2 Aetiology of heart failure in Europe

Chronic heart failure may be due to myocardial dysfunction (in a vast majority of subjects caused by ischaemic heart disease or arterial hypertension, more rarely by other primary or secondary cardiomyopathies), arrhythmias, valve abnormalities or pericardial disease. Anaemia, renal or thyroid dysfunction and cardio-depressant drugs may exacerbate, or more rarely, cause, heart failure. The aetiology of heart failure will also depend on ethnic origin, socioeconomic status and geographic location.

It still remains unclear which genes are most responsible for heart failure even though patients often report a strong family history for this condition. In very few cases heart failure may have a monogenic basis (as in inherited hypertrophic cardiomiopathy and dilated cardiomiopathy) although in most of the cases it is caused by complex polygenic conditions, such as hypertension and coronary artery disease, where the myocardial dysfunction is ultimately determined by changes in expression of very many genes within the tissue.
Despite the advances, traditional techniques like molecular and genetic studies have identified only a partial list of genes and genetic markers carrying potential prognostic power, as changes in gene expression extends beyond the pathways that can possibly be identified by such studies. On the contrary, the genomic technologies offer the possibility to compile gene-expression profiles of heart failure in different time and spatial points. By simultaneous scanning, microarrays potentially allow to draw a whole-genome "portrait" of the levels of gene expression. As this will ultimately lead to the identification of genes that can became new diagnostic and therapeutic tools, such functional genomic approach might in the future fill the gaps in the current knowledge on heart failure pathogenesis, progression and drug response.

3 Epidemiology

Estimates of the prevalence of symptomatic heart failure in the general European population range from 0,4% to 2%. The prevalence of heart failure increases rapidly with age with the mean age of the heart failure population being 74 years. The European Society of Cardiology represents countries with a total population of over 900 million, suggesting that there are at least 10 million patients with heart failure in those countries.

4 Pathophysiology of heart failure

Heart failure is a complex clinical syndrome where the heart is unable to pump sufficient blood to cover the body's metabolic needs. This is associated by an activation of a number of physiological mechanisms (listed in Table-1) aimed

at counteracting the reduction in blood supply, although in the long run many of them actually aggravate the condition (Table-2).

The development of heart failure signs and symptoms is due to two factors:

1. Reduction in cardiac output. It is mainly responsible for fatigue, hypotension (low blood pressure, in more severe cases), changes in renal function due to hypoperfusion.
2. Activation of compensatory mechanisms. They may lead to tachycardia (increased heart rate), peripheral vasoconstriction (pale, cold skin), fluid retention and increased pulmonary and systemic venous pressure (pulmonary and peripheral oedema, liver enlargement, jugular veins distension)

The main compensatory mechanism includes:

1) Autonomic nervous system (mainly an activation of sympathetic nervous system). As a physiological response it maintains blood pressure level required for an adequate blood supply to vitally important organs (brain, heart) through an increased cardiac output (increase in heart rate, myocardial contractility, and rate of myocardial relaxation; increased venous return due to venous vasoconstriction) and systemic vascular resistance (SVR – due to peripheral arterial vasoconstriction). In heart failure, however, it increases the oxygen demand of the heart (particularly relevant in patients with ischaemic heart disease), induces death of myocytes and may cause life threatening arrhythmias.

2) Renin-angiotensin-aldosterone system (RAAS). Activated mainly as a response to a reduced renal perfusion is an important physiological mechanism counteracting the reduction in plasma volume. In response it induces sodium and water retention in the kidneys, causes arterial and venous vasoconstriction (angiotensin) and may directly enhance myocardial contractility. In heart failure it contributes to fluid overload, increases afterload and may induce cell death (angiotensin) and myocardial fibrosis (aldosterone) aggravating the pathological changes in the structure of myocardium.

3) Haemodynamic compensatory mechanism (Frank-Starling law of the heart): an increase of end-diastolic length of cardiac myocytes results in an increased strength of contraction and therefore the larger the end-diastolic volume of ventricle, the higher its stroke volume. Physiologically it is aimed at maintaining the balance between the cardiac output and venous return (by increasing the volume of ejected blood in response to an increased influx of blood into the ventricle). In heart failure it allows the maintenance of adequate stroke volume (i.e. cardiac output) owing to an increase in end-diastolic volume. This, however, occurs at a cost of an increase in filling pressure, which is transferred backwards in a vascular bed and may lead to pulmonary and peripheral oedema. Moreover according to the Laplace relationship, an increased radius of the ventricle in combination with increased transmural pressure and inadequate wall thickening

(see below) leads to an increase in wall tension, which in turn translates into an increased work of the muscle with elevated oxygen demand.

4) Cardiac hypertrophy. The changes in the structure of left ventricle in heart failure occur in response to a prolonged volume overload, myocardial ischaemia (e.g. postinfartion remodelling), pressure overload (hypertension) and neurohormonal stimulation (RAAS, sympathetic nervous system). They include an increase in the internal diameter of left ventricle (LV dilatation), hypertrophy of cardiomyocytes (not accompanied by an increase in their number or in the number of capillaries that supply the myocardium) and proliferation of fibrous tissue in the myocardium (fibrosis). Initially the hypertrophy and to some extent also dilation maintain the contractile function of the myocardium. With time, however, a progressive LV dilation and fibrosis as well as a gradual loss of myocytes lead to a progressive dysfunction of heart as a pump.

A number of other compensatory mechanisms in HF occur that can affect the myocardium, kidneys, smooth and skeletal muscles, endothelium, peripheral vasculature, and multiple reflex control mechanisms, adding to the complexity of the syndrome. Among them are many neurohormones that circulate in abnormal quantities in HF. The natriuretic peptides – atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) can reduce the right atrial pressure, systemic vascular resistance, RAAS activation and aldosterone secretion, sympathetic nerve stimulation and norepinephrine release and hypertrophy of cells and can enhance sodium excretion. Thus they counteract most neurohormonal mechanisms activated in HF and characterized by vasoconstriction coupled with salt and water retention. Whereas ANP is normally synthesized in the atria, BNP is mainly synthesized by ventricles and it has been used as a marker for asymptomatic LV dysfunction or early heart failure.

Other humoral factors involved in HF pathogenesis include arginine vasopressin (AVP), endothelins and prostaglandins but their function is less well understood.

1) Autonomic nervous system
   - Heart
     - Increased heart rate
     - Increased myocardial contractile stimulation
     - Increased rate of relaxation
   - Peripheral circulation
     - Arterial vasoconstriction (increased afterload)
     - Venous vasoconstriction (increased preload)

2) Kidney (renin-angiotensin-aldosterone)
   - Arterial vasoconstriction (increased afterload)
   - Venous vasoconstriction (increased preload)
   - Sodium and water retention (increased preload and afterload)
   - Increased myocardial contractile stimulation

3) Endothelin-1 (increased preload and afterload)
4) Arginine vasopressin (increased preload and afterload)
5) Atrial and brain natriuretic petides (decreased afterload)
6) Prostaglandins
7) Frank-Starling law of the heart
   - Increased end-diastolic fibre length, volume, and pressure (increased preload)

8) Hypertrophy of left ventricle
9) Peripheral oxygen delivery
   - Redistribution of cardiac output
   - Altered oxygen-hemoglobin dissociation
   - Increased oxygen extraction by tissues

10) Anaerobic metabolism

Table-1: Compensatory mechanisms in heart failure

	Short-term adaptive response	**Long-term maladaptive response**
Salt and water retention	↑Preload ↑Cardiac output	Edema, pulmonary congestion
Vasoconstriction	↑Afterload Maintained blood pressure	↓Cardiac output ↑Cardiac energy expenditure Cell death
↑Cardiac adrenergic drive	↑Contractility ↑Relaxation ↑Heart rate ↑Cardiac output	Arrhythmias ↑Cardiac energy expenditure Cell death
Transcription factor activation **Cell growth**	Adaptive hypertrophy ↑Sarcomere number ↑Cardiac output	Maladaptive hypertrophy Apoptosis Mitochondrial DNA abnormalities Cell death

Table-2: Adaptive and maladaptive role of compensatory mechanisms initiated by low cardiac output in heart failure

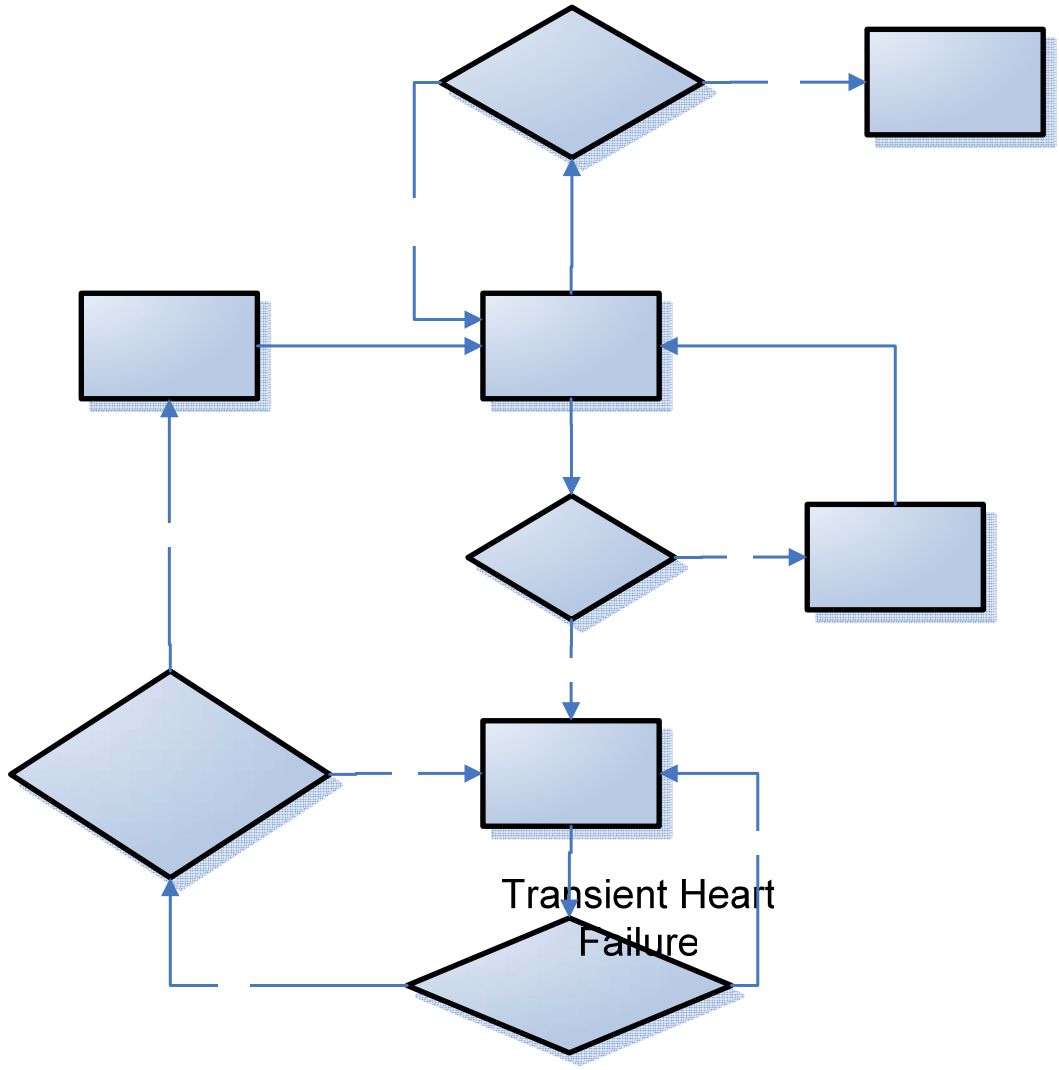

Figure – 1: Relation between heart failure, symptoms and cardiac dysfunction.

5 Diagnosis in Heart Failure

5.1 Practical assessment of patients

1) Initial Evaluation of Patients and Detection of Predisposing Conditions
Identification of Patients:

- with a syndrome of decreased exercise tolerance;
- with a syndrome of fluid retention;
- or with no symptoms and incidentally discovered left ventricular dysfunction.

2) Identification of Structural Abnormality

- A complete history and physical examination;
- Echocardiography, coupled with Doppler flow studies;
- Chest radiography
- 12-lead electrocardiogram
- The measurement of circulating levels of brain natriuretic peptide (BNP)

3) Evaluation of the Cause of Ventricular Dysfunction.

- Evaluation of potential causative factors should include patient and family history, general laboratory testing (complete blood count, urinalysis, all serum electrolytes, blood urea nitrogen, serum creatinine, blood glucose, liver function tests, and thyroid stimulating hormone), evaluation of the possibility of coronary artery disease, and evaluation of the possibility of primary myocardial disease.

4) Ongoing Evaluation of HF

- The ongoing review of the patient's clinical status is critical to the appropriate selection and monitoring of treatment. It should include assessment of functional capacity, assessment of volume status, laboratory evaluation (serial monitoring of serum electrolytes and renal function), and assessment of prognosis.

Symptoms and signs are important as they alert the observer to the possibility that HF exists. The clinical suspicion of heart failure must be confirmed by more objective tests particularly aimed at assessing cardiac function.
First-line exams (if they are normal heart failure diagnosis can be excluded) include:

- electrocardiogram (ECG)
- chest X-ray
- echocardiography
- BNP level

If their results are abnormal, then other second-line exams should be performed.

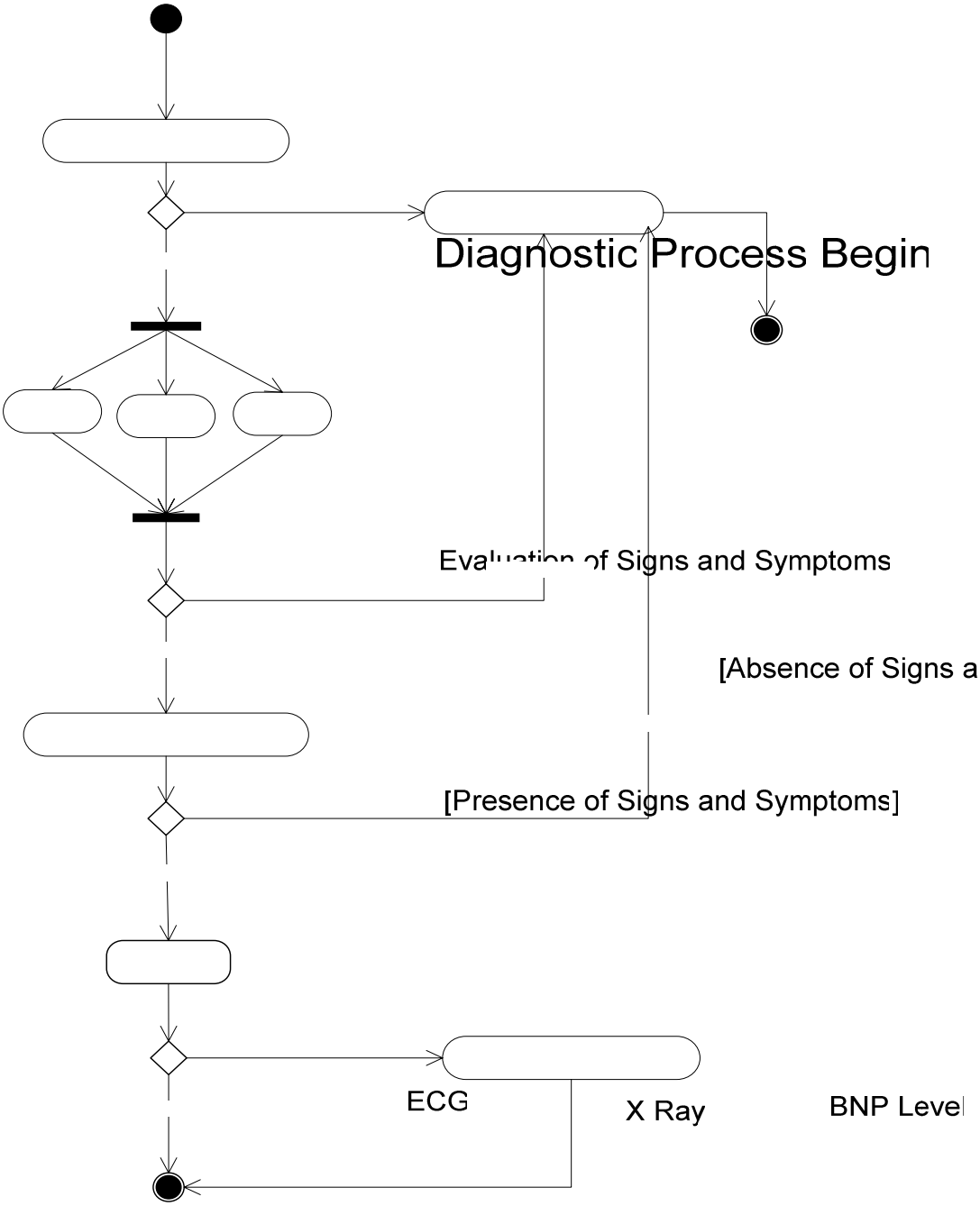

Figure – 2: Diagnostic Process

5.2 Exams used in the diagnostic process

5.2.1 Symptoms and signs of heart failure

Main sign and symptoms:

- breathlessness (dyspnea)
- ankle swelling (peripheral oedema)
- fatigue

Other signs and symptoms: hepatomegaly, elevated jugular venous pressure, tachycardia, a third heart sound, pulmonary crepitations.

Symptoms and signs	
When to perform during diagnosis	At first visit
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN SYMPTOMS, AT EVERY VISIT
When to perform during follow up	In every visit
Which parameters	Breathlessness, swelling, fatigue, hepatomegaly, elevated jugular venous pressure, tachycardia, a third heart sound, pulmonary crepitations.

5.2.2 Electrocardiogram

The most relevant findings include the presence of anterior Q waves and a left bundle branch block, signs of left atrial overload or left ventricular hypertrophy, atrial fibrillation or flutter, ventricular arrhythmia.

Electrocardiogram	
When to perform	At first ambulatory visit.
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN SYMPTOMS, AND AT EVERY VISIT
When to perform during follow up	AT EVERY VISIT
Which parameters	Anterior Q waves, left bundle branch block, left ventricular hypertrophy, atrial fibrillation or flutter, ventricular arrhythmia
Which information the exam provides	If Symptoms and signs and ECG abnormalities are present CHF is carefully possible, otherwise diagnosis should be reviewed.

5.2.3 The chest X-ray

The investigation is useful to detect the presence of cardiac enlargement (cardiothoracic ratio >0·50) and pulmonary congestion.

The chest X-ray	
When to perform	Initial diagnostic work-up in HF
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN RESPIRATORY SYMPTOMS; AT FINAL VISIT
When to perform during follow up	At changes in respiratory symptoms and signs.
Which parameters	cardiothoracic ratio >0·50, pleural effusion, congestion, interstitial and alveolar oedema.
Which information the exam provides	If symptoms and signs and ECG abnormalities and X-ray findings are present HF is carefully possible, otherwise diagnosis should be reviewed.

5.2.4 Echocardiography

Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest. It's important not only for diagnosis of new appearance of heart failure, but also for heart failure follow-up. The most important parameter of systolic left ventricular function in HF is the left ventricular ejection fraction (LVEF). Information on diastolic function of the left ventricle, frequently altered in elderly patients with CHF, is also important. It can be derived from Doppler measurement (isovolumic relaxation time, early to atrial left ventricular filling ratio, early left ventricular filling deceleration time, pulmonary venous atrial flow velocity duration and ratio of pulmonary vein systolic and diastolic flow velocities) on cardiac filling characteristics. The degree of secondary tricuspid regurgitation gives an estimate of pulmonary artery pressures.

Echocardiography	
When to perform	As first line exam to perform diagnosis of HF.
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN SYMPTOMS; AT FINAL VISIT
When to perform during follow up	At changes in symptoms
Which parameters	Left ventricular ejection fraction (LVEF; n.v. >40%), fractional shortening, sphericity index, atrioventricular plane displacement myocardial performance index, and left ventricular wall motion

	index, isovolumic relaxation time, early to atrial left ventricular filling ratio, early left ventricular filling deceleration time, pulmonary venous atrial flow velocity duration and ratio of pulmonary vein systolic and diastolic flow velocities, pulmonary artery pressures.
Which information the exam provides	If symptoms and signs and ECG / X-ray / Echocardiographic abnormalities are present HF is present.

5.2.5 Haematology and biochemistry

The following laboratory investigations are recommended as part of a routine diagnostic evaluation of patients with chronic heart failure: Complete blood count (Hb, leukocytes, platelets), electrolytes (sodium, potassium), S-creatinine, S-glucose, S-hepatic enzymes and urinalysis. Additional tests to consider include: C-reactive protein (CRP), thyroid stimulating hormone (TSH), S-uric acid and S-urea.

Haematology and biochemistry	
When to perform	At first visit
When to perform during HEARTFAID	AT BASELINE ONLY AND AT CHANGES IN SYMPTOMS; AT FINAL VISIT
When to perform during follow up	At changes in symptoms, when drug therapy is modified.
Which parameters	Complete blood count (Hb, leukocytes, platelets), S-electrolytes (sodium, potassium), S-creatinine, S-glucose, S-hepatic enzymes and urinalysis; C-reactive protein (CRP), thyroid stimulating hormone (TSH), S-uric acid and S-urea.
Which information the exam provides	Laboratory indicators of organ damage (creatinine, hyperkalemia, bilirubine, AST, ALT, CPK, anaemia, etc) indicate a bad prognosis and may be used to optimized therapeutic choice.

5.2.6 Neuroendocrine evaluations

Tests of neuroendocrine activation are: natriuretic peptides that can be helpful in the diagnostic process, especially in untreated patients; circulating levels of noradrenaline, renin, angiotensin II, aldosterone, endothelin-1 and adrenomedullin are related to the severity and prognosis of heart failure, but in individual patients these predictors are inaccurate and difficult to interpret.

Neuroendocrine evaluations	
When to perform	If available, during the initial assessment of cardiac disease
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN SYMPTOMS; AT FINAL VISIT
When to perform during follow up	If a prognostic evaluation is needed
Which parameters	B natriuretic peptides (BNP) level NT – proBNP level
Which information the exam provides	High levels of natriuretic peptides suggest: • the presence of a cardiac disease or, more rarely, the presence of a renal impairment • a worse prognosis Low or normal levels of natriuretic peptides in patients without therapy suggest: • that probably HF is not the cause of the symptom • a better prognosis

5.2.7. 24 h Holter ECG monitoring

Conventional 24 hour Holter ECG monitoring may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias, which could be causing or exacerbating symptoms of heart failure. It also allows the measurement of heart rate variability (HRV), a marker of autonomic balance.

Holter electrocardiography	
When to perform	It is not useful for diagnosis, but it can be performed if arrhythmias is present, but also in absence of them, to assess HRV.
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN ARRHYTHMIA RELATED SYMPTOMS; AT FINAL VISIT
When to perform during follow up	If arrhythmias are suspected.
Which parameters	atrial and ventricular arrhythmias, heart rate variability.
Which information the exam provides	It may be used to optimize therapeutic choice.

5.2.8 Pulmonary function

Forced vital capacity (FVC) is also a valid marker for evaluation of severity (level) and therapy in patients with chronic heart failure.

Pulmonary function	
When to perform	If HF diagnosis is uncertain
When to perform during HEARTFAID	AT BASELINE AND AT CHANGES IN RESPIRATORY SYMPTOMS; AT FINAL VISIT
When to perform during follow up	At changes in respiratory symptoms.
Which parameters	Forced vital capacity, forced expiratory volume, peak expiratory flow rate
Which information the exam provides	It may be used to optimized therapeutic choice.

5.2.9 Additional non-invasive tests to be considered

In patients in which echocardiography at rest has not provided enough information and in patients with coronary artery disease e.g. severe or refractory chronic heart failure and coronary artery disease, further, non-invasive imaging may include: spiroergometric exercise test (with measurement of peak VO_2), stress echocardiography, nuclear cardiology, cardiac magnetic resonance imaging.
The main application of spiroergometric exercise testing is focused on functional and therapeutic assessment and on prognostic stratification.
Performance of cardiopulmonary stress testing is of particular importance, insofar it allows the assessment of exercise capacity with gas exchange measurement and has proved to be an important component of the risk profile in HF. A peak VO2 <10 mL/kg per min identifies high risk and a peak VO2 >18 mL/kg per min identifies low risk patients. Value between these cut off limits define a grey zone of medium risk patients without further possible stratification by VO2. Assessment of the ventilatory response to exercise, measured as the slope of the relation between minute ventilation and carbon dioxide production during exercise has been shown to have an independent prognostic value in CHF. In recent studies, its may have prognostic value superior to that of peak VO2.

5.2.10 Invasive investigation

Three diagnostic tools may be helpful in different situations: coronary angiography, haemodynamic monitoring and endomyocardial biopsy. None of them is indicated as a routine procedure.

6 Prognosis in Heart Failure

6.1 The prognostic evaluation

The problem of defining prognosis in HF is complex for many reasons: several aetiologies, frequent comorbidities, varying individual progression, outcome and treatment efficacy. The variables more consistently indicated as independent negative outcome predictors are reported in table below.

Table-3: Independent predictors of a worse prognosis

Demografics and Historical	***Clinical***	***Electrophysiologic***	***Functional***	***Blood***	***Haemodinamic***
Advanced age	High heart rate	Broad QRS	VO2 max (mL/Kg x min< 10-14)	High serum BNP	Low Left ventricular EF
Coronary aetiology	Persist low Blood Pressure	Low heart rate variability	Low 6 min walking ability	High serum norepinephrine	Increased LV volumes
Diabetes	NHYA III-IV	Complex ventricular rhythms	High VE/VCO2 ratio	Low serum sodium	Low cardiac index
Resuscitated sudden death	Involuntary weight loss	T-wave alternans		High serum creatinine	High left ventricular filling pressure
Ethnic group	Ventilatory rhythm and rate disturbance			High serum bilirubine	Restrictive mitral filling pattern
				Anaemia	Impaired right ventricular function
					Cardiothoracic ratio

6.2 Known rules for the prognostic decision

Prognostic stratification must be useful for making therapeutic decisions. Unfortunately poor information are available in order to evaluate the patient prognosis. Below main prognostic markers and the situations when they are relevant are listed:

- left ventricular ejection fraction - in asymptomatic patients with left ventricular dysfunction, less so in advanced heart failure
- plasma volume changes over time and the onset or worsening of mitral regurgitation
- brain natriuretic peptide (but not other measures of neurohormonal activation), less so in advanced HF
- central haemodynamic pattern and right ventricular function - in severe heart failure (in particular if right ventricular function deteriorates, the clinical situation can worsen dramatically and alternative treatments should be considered).

- parameters indicating organ damage (elevated blood levels of creatinine or bilirubine, hyponatremia and neurohormonal activations) - in advanced heart failure. In particular, renal dysfunction has emerged as one of the most potent risk markers in HF
- pulmonary resistance - in advanced HF.
- A markedly reduced exercise capacity in optimized therapy is a parameter traditionally used in HF as an indicator of irreversible cardiovascular compromise. It should probably be complemented with other parameters such as VE/VCO2 slope.

7 Management of heart failure

The disease-management approach views HF as a chronic illness that spans the home as well as outpatient and inpatient setting. Most patients have multiple medical, social, and behavioural challenges, and effective care requires a multidisciplinary system approach that addresses these various difficulties. Heart failure disease-management programs need to include intensive patient education, encouragement to be more participant in their care, close monitoring of patients through telephone follow-up or home nursing, careful review of medications to improve adherence to evidence-based guidelines, and multidisciplinary care with nurse case management directed by a physician (usually moderate-high risk patients have been chosen for such programs). Such programs can reduce the frequency of hospitalization and can improve the quality of life and functional status, especially in high risk patents.
Many questions need to be answered in the definition of the most effective system of co-management of patient, however a collaborative model in which specialists with different expertise work together to optimize the care of patient with HF is likely to be most fruitful.
The aims of heart failure management are those of the treatment of any disease in general and consist of several components.

7.1 Prevention of heart failure

The prevention of heart failure should always be a primary objective. It includes management of risk factors for coronary heart disease, treatment of ischaemia, early diagnosis of acute myocardial infarction, prevention of reinfarction, accurate identification and proper control of hypertension (<140/90mmHg) and some causes of specific heart muscle disease and correction of valve disorders and congenital heart disease. The second objective of modern therapy is to modulate progression from asymptomatic left ventricular dysfunction to heart failure.
The therapeutic approach in chronic heart failure due to systolic cardiac dysfunction consists of general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices and surgery.

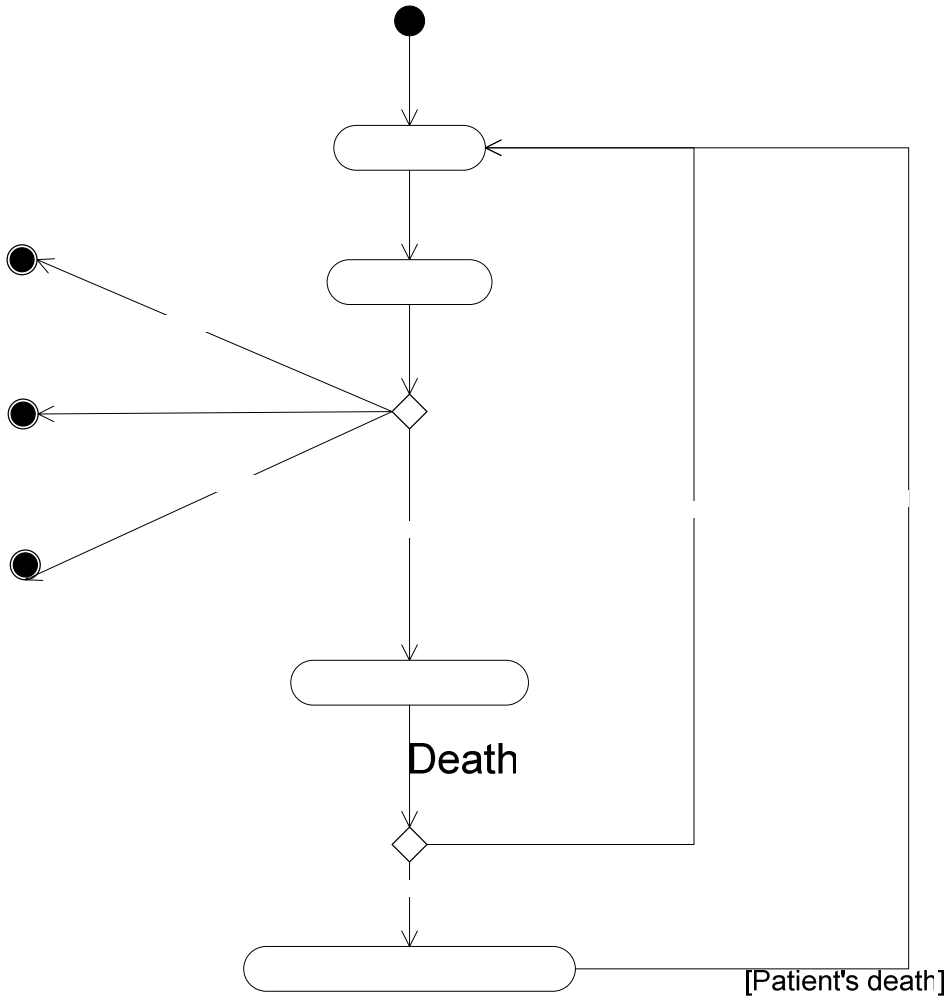

Figure – 3: Therapeutic process

7.2 Non-pharmacological management

7.2.1 Weight control.

Patients are advised to weigh themselves on a regular basis (once a day, twice a week) and, in case of a sudden unexpected weight gain of more than 2 kg in 3 days, to alert a health care provider or adjust their diuretic dose accordingly, e.g. to increase the dose if a sustained increase is noted.

7.2.2 Dietary measure.

Controlling the amount of salt in the diet is a problem that is more relevant in advanced heart failure than mild failure. Salt substitutes must be used with caution, as they may contain potassium. In large quantities, in combination with an ACE inhibitor or aldosterone antagonist they may lead to hyperkalaemia. *Fluids*: Fluid intake must be reduced in patients with advanced heart failure, with or without hyponatremia. The exact amount of fluid restriction remains unclear. In practice, a fluid restriction of 1,5–2 litres is advised in advanced heart failure. *Alcohol*: Moderate alcohol intake is permitted. Alcohol consumption must be prohibited in suspected cases of alcoholic cardiomyopathy.

7.2.3 Obesity.

Treatment of chronic heart failure should include weight reduction in the overweight or obese. The subject is overweight if his/her body mass index (i.e. the actual weight in kilograms divided by height in meters squared) lies between 25 and 30 and obese if it is >30.

7.2.4 Abnormal weight loss.

Clinical or subclinical malnutrition is present in about 50% of patients with severe chronic heart failure. The wasting of total body fat and lean body mass that accompanies weight loss is called cardiac cachexia. Cardiac cachexia is an important predictor of reduced survival.

7.2.5 Smoking.

Smoking should always be discouraged.

7.2.6 Sexual activity.

Advise, if appropriate, the use of sublingual nitrates before sex and discourage major emotional involvements. Patients in NYHA class II are at intermediate risk and class III-IV are at high risk of cardiac decompensation triggered by sexual activity.

7.2.7 Drugs to avoid or beware.

The following drugs should be used with caution when co-prescribed with any form of heart failure treatment, or avoided: non-steroidal antiinflammatory drugs (NSAIDs), class I antiarrhythmics, calcium antagonists (verapamil, diltiazem, first generation dihydropyridine derivatives), tricyclic antidepressants, corticosteroids, lithium.

7.2.8 Rest, exercise and exercise training.

Rest should not be encouraged in stable chronic heart failure. When there is acute heart failure or destabilization of chronic heart failure, physical rest or bed-rest is necessary. Passive mobilization exercises are carried out in order to prevent untoward effects resulting from prolonged bed-rest and attenuate the risk of venous thrombosis. As the clinical condition of the patient improves, respiratory exercises and active mobilization can be carried out. If in a stable condition, the patient should be encouraged to carry out daily physical and leisure time activities that do not induce symptoms, to prevent muscle de-conditioning. Strenuous or isometric exercises and competitive and tiring sport should be discouraged. If the patient is employed, the work tasks carried out must be assessed and advice given on whether they can be continued. Exercise training programmes are encouraged in stable patients in NYHA class II–III.

7.3 Pharmacological therapy

7.3.1 Angiotensin-converting enzyme inhibitors

They are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e. <40%.

ACE inhibitors	
When recommended	First-line therapy in patients with subnormal ejection fraction (<40–45%)
How to optimize the therapy	It should be gradually up-tritated from lower dose level to target dose
Which parameters should be checked	Blood pressure, heart rate, renal function (creatinine and creatinine clearance calculated by Cockroft and Gault formula[1]), serum electrolytes 1-2 weeks after each doses increment, at 3 months and subsequently at 6 regular monthly intervals.

[1] **Cockroft and Gault formula:** Creatinine clearance (ml/min)= (140-age)x weight (kg) x 1.22/serum creatinine (μmol/L). Value should be reduced by 15% for women.

7.3.2 Diuretics

Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance. Diuretics should always be administered in combination with ACE inhibitors if possible. Thiazides are less effective then loop diuretics if glomerular filtration rate (GFR) < 30 ml/min. Potassium-sparing diuretics (spironolactone) should only be prescribed if hypokalaemia persists despite ACE inhibition or, in severe heart failure despite the treatment with ACE inhibitor and diuretic.

Diuretics	
When recommended	In association with ACE-inhibitors with fluid overload (pulmonary congestion or peripheral oedema)
How to optimize the therapy	If GFR< 30 mL/min use loop diuretics. If an insufficient response is present: use a synergic therapy (loop diuretics + thiazides), increase dose of loop diuretics twice daily, if hypokalaemia persists after initiation of ACE inhibitors and diuretics add potassium-sparing diuretics (spironolactone) initiating with 1-week low dose administration. During diuretics treatment check serum potassium and creatinine after 5-7 days and titrate accordingly. Recheck every 5-7 days until potassium values are stable.
Which parameters should be checked	Improvement of dyspnoea and increased exercise tolerance, blood pressure, heart rate, renal function, electrolytes
Spironolactone	Aldosterone Antagonist
When recommended	A patient is in severe HF (NHYA III-IV) despite ACE inhibition/diuretic therapy.
How to optimize the therapy	12,5-25 mg/daily
Which parameters should be checked	Check serum potassium and creatinine after 4-6 days, if serum potassium 5-5,5 mmol/L, reduce dose by 50%. Stop if serum potassium >5,5 mmol/L. If after 1 months symptoms persist and normokalaemia exists, increase to 50 mg/daily and check potassium and creatinine after 1 week

7.3.3 Beta-adrenoceptor antagonists

Beta-adrenoceptor antagonists (beta-blockers) are recommended for the treatment of all patients with stable, from mild to severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction, in NYHA class II to IV, on standard treatment, including diuretics and ACE inhibitors, unless there is a contraindication.

Beta antagonists	
When recommended	Patients with stable, mild to severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction, in NYHA class II to IV, on standard treatment, including diuretics and ACE inhibitors.
How to optimize the therapy	It should be gradually up-tritated from lower dose level to target dose, doubling every 3 weeks (i.e.: carvedilol)

Which parameters should be checked	Blood pressure, heart rate, ECG abnormalities.

7.3.4 Angiotensin II receptor antagonists

ARBs could be considered in patients who do not tolerate ACE inhibitors for symptomatic treatment. However, it is unclear whether ARBs are as effective as ACE inhibitors for mortality reduction. In combination with ACE inhibition, ARBs may improve heart failure symptoms and reduce hospitalizations for worsening heart failure.

ARBs	
When recommended	As an alternative to ACE-inhibition in symptomatic patients intolerant to ACE-inhibitors to improve morbidity and mortality. ARBs and ACE-inhibitors have similar efficacy on mortality in acute myocardial infarction with signs of heart failure or left ventricular dysfunction. In combination with ACE-inhibitors in patients who remain symptomatic to reduce mortality.
How to optimize the therapy	It should be gradually up-tritated from lower dose level to target dose (i.e.: candesartan, from 4 mg/daily to 32 mg/daily)
Which parameters should be checked	As ACE-inhibitor

7.3.5 Cardiac glycosides

Cardiac glycosides (digoxin) are indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not left ventricular dysfunction is the cause, in order to slow ventricular rate, thereby improving ventricular function and symptoms.

Cardiac glycosides	(digoxin)
When recommended	atrial fibrillation and/or symptomatic heart failure
How to optimize the therapy	0,125-0,250 mg/daily, in the elderly 0,0625-0,125 mg/daily
Which parameters should be checked	Renal function (creatinine and creatinine clearance) and plasma potassium

7.3.6 Antithrombotic agents.

There is little evidence to show that antithrombotic therapy modifies the risk of death, or vascular events in patients with heart failure other than in the setting of atrial fibrillation when anticoagulation is firmly indicated, and prior myocardial infarction when either aspirin or oral anticoagulants should be used as secondary prophylaxis.

7.3.7 Antiarrhythmics

In general, they are no indicated in heart failure. Indications for antiarrhythmic drug therapy in the individual patient include atrial fibrillation (rarely flutter), non-sustained or sustained ventricular tachycardia.

7.4 Devices and surgery

It includes revascularization procedures, resynchronization therapy, mitral valve surgery, cardiomyoplasty, arrhythmia devices and surgery, ultrafiltration.

7.5 Choice and timing of pharmacological therapy

7.5.1 Asymptomatic systolic left ventricular dysfunction.

Treatment with an ACE inhibitor or beta-blockers is recommended.

7.5.2 Symptomatic systolic left ventricular dysfunction (NYHA II).

Without signs of fluid retention: ACE inhibitor and Beta-blockers. With signs of fluid retention: diuretics in combination with an ACE inhibitor and a beta-blocker.

7.5.3 Worsening heart failure.

Patients in NYHA class III who have improved from NYHA class IV during the preceding 6 months or are currently NYHA class IV should receive low-dose spironolactone. Cardiac glycosides are often added. Loop diuretics can be increased in dose. Combinations of diuretics (a loop diuretic with a thiazide) are often helpful.

7.5.4 End-stage heart failure

Patients should be (re)considered for heart transplantation. In addition to the common pharmacological treatments, intermittent inotropic support can be used.

7.6 Care and follow-up

Different models (e.g. heart failure outpatient clinic, heart failure nurse specialist, community nurse specialist, patient tele-monitoring) may be appropriate, depending on the stage of the disease, patient population and national resources, to improve quality of life, reduce readmission and decrease cost.

8 Problem Statement and formulation of the relevant Decision Making Problems

The HEARTFAID project aims at developing a technological platform serving patients with CHF, the medical personnel involved in their management as well as patients' relatives involved in their care, all of them acting in their respective environments. The organization of this technological platform is outlined in Fig.4. This organization is solely functional, with services tailored to the CHF domain.

Procedures (columns). Briefly, this innovative form of decision and informative support will help with procedures related to:

- *diagnosis* of CHF;
- clinical *standard management* and *prognosis* assessment of patients with CHF according to the most recent European Society of Cardiology (ESC) Guidelines (*European Heart Journal 2005; 26:1115-1140; European Heart Journal 2005; 26:384-416*);
- *research and development* in the medical and technical areas of knowledge overall pertaining to the CHF domain.

Procedures regarding *management* and *research* overlap: in fact, during the follow-up phase, while supporting the standard CHF management and prognosis assessment, the HEARTFAID Platform (HFP) will assist in collecting biomedical information for research and development purposes.

Environments (rows). With the current project we plan on developing a tool capable of collecting, integrating, and processing relevant biomedical data and information coming from the main settings actually encountered by patients with CHF.
These settings include:

- the *medical environment*, corresponding to HFP level of functioning 1 (i.e. office of the general practitioner), and HFP level 2 (i.e. specialized hospital, with cardiologists involved in outpatient and inpatient care, and with the possibility of running a variety of tests, such as blood tests, EKG, X-Rays, ultrasound imaging studies, etc);
- the *patient environment*, (i.e. patient's home) corresponding to HFP level 3;
- the medical and technological *research environment*, corresponding to HFP level 4.

A future development may be the HFP level 5, where data coming from a number of platforms (levels 1-4) might be integrated at the national or international level (i.e. randomized clinical trials, public health).

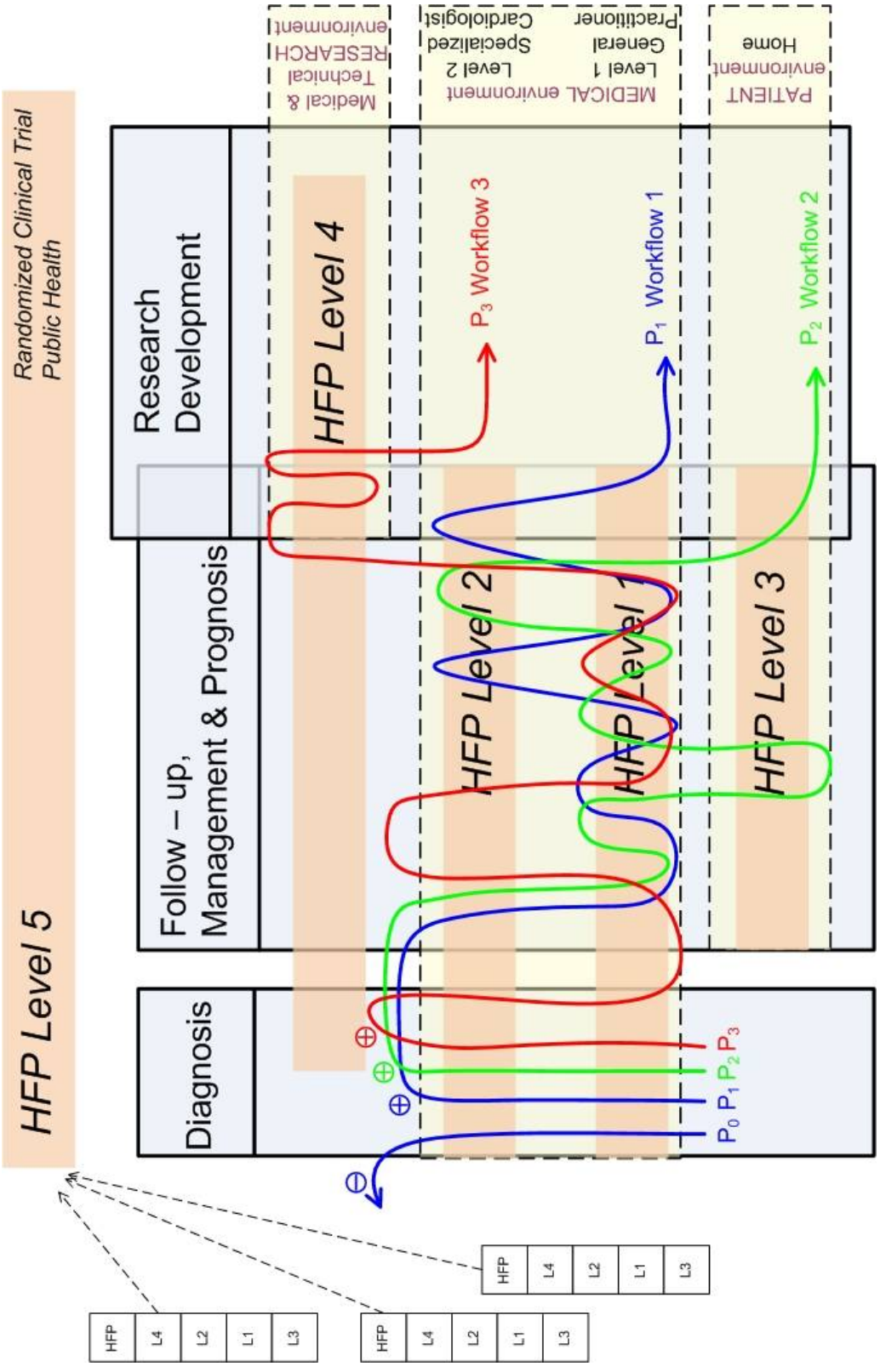

Figure – 4: Organization of the HEARTFAID technological platform (HFP).

The basic levels of functioning of the HF platform are articulated in various workflows.

- **Workflow 1: medical environment.**

In Fig 4. HFP level 1 and 2 and patients n. 0 and n. 1.

Processes of diagnosis, management, prognosis assessment with patients' data collected and medical recommendations provided both in the office of the family physician and in the specialized cardiology setting.

- **Workflow 2: medical environment and patient's home.**

In Fig 4. HFP level 1, 2 and 3 and patient n. 2.

Processes of diagnosis, management, prognosis assessment, with patients' data collected and medical recommendations provided, as above, both in the office of the family physician and in the specialized cardiology setting.

Of notice, biomedical parameters, relevant symptoms and compliance to prescribed pharmacological and non pharmacological regimens will be monitored by HFP level 3 in patients' homes.

Serial measurements of selected biological parameters will be collected by the patients and by their relatives and will enter HFP level 3.

Furthermore, HFP level 3 will engage with the patients by providing informative material, reminders on medications' schedule, reminders on biomedical measurements.

- Workflow 3: medical environment (HFP level 1 and 2) and research environment (either medical or technical) (HFP level 4).

Processes of diagnosis, management, prognosis assessment with patients' data collected (and medical recommendations provided) in the office of the family physician, in the specialized cardiology setting, and in the ultraspecialized research setting.

As stated above, in workflow 3, while supporting the standard CHF management and prognosis assessment, the HFP will assist in collecting biomedical information for research and development purposes.

More sophisticated biomedical data entering the HF platform at this level may include, for example, continuous non invasive heart rate and beat-by-beat blood pressure measurement. The HFP might in future acquire data regarding innovative heart imaging studies, more thorough heart functional studies (as the cardiopulmonary test with breath-by-breath assessment of O^2 consumption

and CO^2 production, etc). This level will collect the largest variety of biomedical data.

Given the flexibility of the HFP, other Workflows are conceivable, for example for patients entering HFP levels from 1 to 4.

8.1 Problem Statement and formulation of the Decision Making Problems relevant to Workflow 1.

8.1.1 Diagnosis of Chronic Heart Failure (CHF).

According to the ESC Guidelines on CHF, as there is NO ONE cutoff value in ONE single test that can be used reliably to identify patients with heart failure.

According to the ESC guidelines, the diagnosis of HF relies on clinical judgment based on:

- ***symptoms*** (one or more, complained by the patient) **and/or *signs*** (one or more, detected by the physician during the physical examination) of HF (at rest and during exercise)

AND

- objective evidence coming by ***tests*** (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) at rest.

A ***response to treatment*** directed towards heart failure is not necessary although supportive of HF diagnosis. HF patients should show some improvement in symptoms and signs with treatment.

Symptoms include: breathlessness (i.e. shortness of breath, worse with exertion and/or supine position), fatigue (worse with exertion),.

Signs include: peripheral oedema, ankle oedema, hepatomegaly, raised jugular venous pressure, pulmonary crepitations, third heart sound.

Tests include:

- ECG:
if normal it has a predictive negative value to exclude left ventricular systolic dysfunction of > 90%;
if abnormal (see section 5.2.2 for list of abnormalities) it has little predictive value for the presence of heart failure.

- chest X-Ray
X-ray findings have value ONLY in the context of typical symptoms and signs and of abnormal ECG.

Abnormal findings (see section 5.2.3.) are useful indicators of decreased left ventricular systolic function.

Of note, among abnormal chest X-Ray findings, an increased cardiac size (cardiomegaly), as judged by a cardiothoracic ratio > 0.5, may be frequently absent in acute HF, left ventricular systolic and diastolic HF.

- Natriuretic peptides
Plasma concentrations of certain natriuretic peptides and their precursors (especially BNP and NT-proBNP) are very helpful in diagnosis.

Today, in clinical practice, their place is as "rule out" tests, to exclude significant cardiac disease.
There is a direct relationship between increasing plasma concentration of natriuretic peptides and decreasing (usually left ventricular) function, although no clear cut diagnostic thresholds are available.

A low-normal concentration in an untreated patient cannot completely exclude a cardiac disease, but makes HF unlikely to be the cause of symptoms. In a population with a high a priori probability of heart failure the negative predictive value of BNP can be as high as 97% and the positive predictive value can be as high as 70%.

The diagnostic potential of natriuretic peptides is lower in the presence of normal systolic function when their elevation can indicate diastolic dysfunction.

- Echocardiography.
Echocardiography is the preferred test for the documentation of cardiac dysfunction at rest (see 5.2.4).

A *systolic dysfunction (or systolic heart failure)* is defined when the left ventricular ejection fraction is below 50%.

A *diastolic dysfunction (or diastolic heart failure)* is defined in the presence of
1) signs and/or symptoms of HF;
2) normal of mildly abnormal left ventricular systolic function (ejection fraction ≥ 45-50%);
3) abnormal left ventricular diastolic properties like relaxation, distensibility and stiffness (see 5.2.4).

- Laboratory test. To rule out either an alternative or an additional diagnosis, the following minimum set of tests is recommended (see section 5.2.5).

1) full blood count: a decrease in blood count may unmask a pre-existing asymptomatic HF; an increase in red blood count suggests that a lung disease might be responsible for shortness of breath.
2) renal function tests:
- a kidney dysfunction mimics some of the signs and symptoms of HF by inducing fluid overload.
- HF and kidney dysfunction coexist because: a) they have common underlying causal diseases (hypertension and diabetes); b) because in HF kidney perfusion and function are secondarily impaired.
3) liver function tests:
- a liver dysfunction mimics some of the signs and symptoms of HF.
- HF and liver dysfunction may coexist because, due to HF, liver is poorly perfused, congested and its function is secondarily impaired.
4) urine analysis (proteinuria and glycosuria) to detect either an underlying kidney disease (from hypertension and/or diabetes) or kidney dysfunction due to HF.
5) electrolytes.
6) thyroid function tests:
Both hyperthyroidism and hypothyroidism may cause HF, mimic some of the signs and symptoms, or may exacerbate an underlying HF.

In Workflow 1:

Patients with a **NEGATIVE diagnostic ESC workup** (example **patient P0**) will not contribute to HFP with any further data.

Patients with a **ESC diagnostic workup POSITIVE for CHF** (example, **patient P1**, in Workflow 1) will enter the follow-up phase. During such phase, their management will be performed, and their prognosis assessed, according to the ESC guidelines on Heart Failure.

Potential contributions of the HFP in the diagnosis of chronic heart failure.
Even when the ESC recommendations for the HF diagnosis are strictly followed, a certain number of cases of HF are missed (false negative) and a certain number of other medical conditions are incorrectly classified as HF (false positive). Moreover, not all of the patients with suspected HF can refer to specialized cardiology hospital to have an accurate diagnosis established.

Problem statement 1. HFP, by collecting, integrating, and processing biomedical data relevant to HF diagnosis may overall increase the number of correct (positive or negative) diagnosis by decreasing both the number of falsely negative and falsely positive diagnosis. Additonally, it may help better defining the diagnosis and the prevalence of heart failure with preserved left ventricular ejection fraction.

Problem statement 2. HFP may help in finding the single biomedical parameter or the combination of parameters (among signs, symptoms, and test results) that best identify subjects affected by HF.

Problem statement 3. HFP may play a role in setting new cutoffs and/or new reference values for individual or combinations of parameters, thus allowing to further increase the diagnostic accuracy in the field of HF.

Problem statement 4. HFP may help in improving the diagnostic capability of low resource medical settings where not all of the expensive diagnostic equipments (e.g. echocardiograph) are readily available, and where the diagnosis of HF originates from simpler and less expensive methods (e.g. history and physical examination, ECG, chest X-ray).
Additionally, it may allow a form of remote consultation by submitting patients' data either from a specialized cardiology setting to another (example for complex cases), or from a non specialized medical setting to a specialized one.

8.1.2 Management of Chronic Heart Failure.

Once the diagnosis of HF is established, the subsequent crucial actions to be taken by the medical personnel (see Fig.1) include:

Action a - The determination of the aetiology (see also section 2) of this condition.

Action b - The assessment of HF symptoms' severity (see also section 5.1) following the New York Heart Association (NYHA) classification:

NYHA Class I	→ No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations.
NYHA Class II	→ Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea.
NYHA Class III	→ Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.
NYHA Class IV	→ Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity.

Action c - Choosing appropriate therapeutic approach (see also section 7.2 – 7.4):

c.1 Systolic left ventricular dysfunction.

→ general advice and non-pharmacological measures
→ pharmacological therapy
→ mechanical devices
→ surgery

with the aims of:

. preventing or controlling diseases (as identified by action a-, mostly hypertension and coronary artery disease) leading to HF,
. preventing progression of HF,
. decreasing morbidity
* by improving quality of life
* by reducing hospital admissions (secondary to acute decompensations of CHF, see below)
. decrease mortality (i.e. prolong life).

→ General advice and non-pharmacological measures: all of the patients.
→Pharmacological therapy: choice and timing is based on symptoms severity (assessed by NYHA Class in subjects with impaired systolic left ventricular function, i.e. with Ejection fraction ≤ 50%).

The ESC algorithm suggests decision-making steps, although individual adjustments must be taken into account.

	For Survival/Morbidity	For Symptoms
NYHA I	ACE-I (ARB if ACE-I intolerant) Aldosterone-antagonist if post-MI Add Beta Blocker if post-MI ↑	Reduce/stop diuretic ↑
NYHA II	↑ ACE-I as first line (ARB if ACE-I intolerant) and titrate to target dose add Beta Blocker and titrate to target dose add Aldosterone antagonist if post-MI ↓	↑ +/- diuretic (with ACE-I) depending on fluid retention + digitalis if atrial fibrillation
NYHA III	↓ ACE-I plus ARB (or ARB alone if ACE intolerant) Beta Blocker add Aldosterone antagonist ↓	+ combination of loop and thiazide diuretics + digitalis if still symptomatic
NYHA IV	↓ Continue ACE-I/ARB Beta-Blocker Aldosterone antagonist	+ combination of loop and thiazide diuretics + digitalis + consider temporary inotropic support

→ Rules and suggested actions for mechanical devices and surgery are beyond the scope of this document, but will be included in the actual HFP.

c.2 Diastolic left ventricular dysfunction. Rules and suggested actions for
→general advice and non-pharmacological measures
→ pharmacological therapy
→ mechanical devices
→ surgery
when available, are beyond the scope of this document, but will be included in the actual HFP.

Action d - Provide counselling and education to the patients and to their relatives.

Action e - Monitor progress and change management accordingly.

During the follow-up phase, patients' progress can be monitored by reassessing:

. NYHA Class
. symptoms and signs

with/without

. echocardiogram, other tests

Irrespective of baseline status, by monitoring NYHA class (or HF symptoms/signs), patients conditions can be defined as being:

e.1 stable.
e.2 improving.
e.3 rapidly worsening → A RAPID (hours, few days) onset or worsening of symptoms and signs secondary to abnormal cardiac function DEFINES, according to the ESC guidelines on the diagnosis and treatment of acute heart failure *(European Heart Journal 2005; 26:384-416)* the ACUTE decompensation of CHF.
e.4 slowly worsening → Worsening of symptoms and signs secondary to abnormal cardiac function occurring over several days or months.

e.3 rapidly worsening → Subjects with acutely decompensated CHF usually need hospital admission.

→ Signs/symptoms (i.e. history and clinical examination) have been proven to sufficiently define clinical profiles with different prognostic implications in acutely decompensated CHF patients (*Nohria A, at al. JACC 2003; 41:1797-1804*).

Four clinical profiles classify the severity of acutely decompensated CHF patients. These four profiles are simply based on the presence/absence of ONE OR MORE signs/symptoms of

adequate perfusion of the peripheral circulation
- weakness, confusion, drowsiness
- paleness with peripheral cyanosis
- cold clammy skin
- low blood pressure or symptomatic hypotension
- narrow proportional pulse pressure (systolic BP – diastolic BP/ systolic BP < 25%)
- filliform arterial pulse
- decreased urine output

congestion
- recent history of orthopnea
- pulmonary rales
- jugular venous distention
- hepatojugular reflux
- ascites
- peripheral edema

		CONGESTION	
		-	+
ADEQUATE PERFUSION	+	**PROFILE A** DRY-WARM	**PROFILE B** WET-WARM
	-	**PROFILE L** DRY-COLD	**PROFILE C** WET-COLD

From best to worst clinical profile

Class I → Profile A
Class II → Profile B
Class III → Profile L
Class IV → Profile C

→ Additionally, the combination of presence/absence + severity of certain signs/symptoms

AND

the value of a few biological parameters

DEFINES

several distinct clinical conditions (with different prognostic implications) in acutely decompensated CHF patients.

Clinical Conditions	**Heart rate** (beats/min)	**SBP** (mmHg)	**Urine Output** (L/day)	**Pulmonary congestion**	**Hypoperfusion**	**End organ hypoperfusion**
I) Acute decompensated congestive heart failure	+/-	Low normal/high	+	Mild	+/-	-
II) Acute heart failure with hypertension/hypertensive crisis	Usually increased	High	+/-	moderate-severe	+/-	+, with central nervous system symptoms
III) Acute heart failure with pulmonary oedema	+	Low normal	+	severe	+/-	-
IVa) Cardiogenic shock/ low output syndrome	+	Low normal	Low	Moderate-severe	+	+
IVb) Severe cardiogenic shock	> 90	< 90	Very low	severe	++	+
V) High output failure	+	+/-	+	mild-moderate	-	-
VI) Right sided acute heart failure	Usually low	Low	+/-	low	+/-, acute onset	+/-

I) Acute decompensated congestive heart failure →
signs and symptoms are mild.

II) Acute heart failure with hypertension/hypertensive crisis →
signs and symptoms of HF
with high blood pressure;
If available echocardiogram → relatively preserved left ventricular function;
chest X-Ray → acute oedema

III) Acute heart failure with pulmonary oedema →
severe symptoms of respiratory distress (oxygen saturation usually < 90% on room air, dyspnea, orthopnea, increased respiratory frequency),
with severe signs of pulmonary congestion (rales).
Chest X-Rays verifies the presence of pulmonary oedema.

IVa-IVb) Low output syndrome/cardiogenic shock/severe cardiogenic shock → no distinction, continuum.
Evidence of reduced peripheral perfusion.
Although there is no clear definition for haemodynamic parameters, it is usually characterized by

- reduced blood pressure (SBP < 90 mmHg or a drop of mean arterial pressure > 30 mmHg)
- and/or low urine output (< 0.5 ml/Kg/h)
- and heart rate > 60 beats/min
- with/without evidence of organ congestion.

V) High output failure →
No evidence of low peripheral perfusion (warm periphery)
Usually characterized by high heart rate (and low SBP in septic shock), pulmonary congestion,

VI) Right sided acute heart failure →
Evidence of low peripheral perfusion
Low blood pressure
Increased jugular venous pressure
Increased liver size

Action f – ALL WORSENING patients call for identification of potential precipitating and exacerbating factors of decompensated CHF.
(ESC guidelines, European Heart Journal 2005; 26:384-416).

(1) Decompensation of pre-existing chronic heart failure (e.g. cardiomyopathy)

(2) Acute coronary syndromes
(a) myocardial infarction/unstable angina with large extent of ischaemia and ischaemic dysfunction
(b) mechanical complication of acute myocardial infarction
(c) right ventricular infarction

(3) Hypertensive crisis

(4) Acute tachiarrhythmia (ventricular tachycardia, ventricular fibrillation, atrial fibrillation or flutter, other supraventricular tachycardia) or Bradycardia.

(5) Appearance or worsening of mitral or tricuspid regurgitation (endocarditis, rupture of chordae tendinae, worsening of pre-existing regurgitation)

(6) Severe aortic valve stenosis

(7) Acute severe myocarditis

(8) Cardiac tamponade

(9) Aortic dissection

(10) Post-partum cardiomyopathy

(11) Non-cardiovascular precipitating factors
(a) lack of compliance with medical treatment
(b) volume overload (salt, liquid) or excessive preload reduction (e.g. diuretics + ACE-inhibitors/nitrates).
(c) infections, particularly pneumonia or septicaemia
(d) severe brain insult
(e) after major surgery
(f) reduction in renal function
(g) asthma
(h) drug abuse
(i) alcohol abuse
(j) phaeochromocytoma

(12) High output syndromes
(a) septicaemia
(b) thyrotoxicosis crisis
(c) anaemia
(d) shunt

Action g – In ALL patients monitor compliance to treatment.

Potential contributions of the HFP in the management of chronic heart failure in Workflow 1.

As outlined, the management of HF is complex and articulated. Several actions are directed not only to HF but also to the medical conditions leading to both chronic HF and to acute decompensation of HF.

There is a strong evidence for a widespread insufficient implementation of the numerous pharmacological and non pharmacological recommended measures for HF. This is responsible for some of the progression of HF and for some of the morbility and mortality rate.

The potential contribution of the HFP in the management of HF patients, and thus in HF outcome, is substantial.

Problem statement 5.
According to the current guidelines the management of HF depends on NYHA Classification (i.e. class of symptoms' severity).

NYHA symptom classification is subjective and difficult to separate from concomitant disease conditions.

HFP may be of great support in the complex task of classification of severity by either guiding the physician through the established rules of NYHA classification or by finding the single biomedical parameter or the combination of parameters (among signs and symptoms ± test results) that better defines different degrees of HF severity.

HFP will then allow to compare the accuracy of NYHA classification with the newly proposed HF severity classifications.

Problem statement 6.
Once the HFP has replicated for each patient the NYHA Classification, it can help suggesting, based on the Guidelines, the numerous pharmacological and non pharmacological recommended measures best applying to each individual patient.

Problem statement 7.
The HFP may help not only in suggesting recommendations but also in verifying implementation of guidelines on pharmacological and non pharmacological measures for HF.

This service of the HFP, on larger scale, might have a strong impact on medical outcome and health care costs.

Problem statement 8.
By collecting, integrating, and processing biomedical data**,** the HFP will offer the possibility of effective and thorough monitoring of patients with HF.

Moreover, HFP may help in finding the single biomedical parameter or the combination of parameters (among signs, symptoms, and test results) that best identifies subjects in stable, improving, rapidly worsening, or slowly worsening conditions.

Problem statement 9.
As for each of the possible conditions (stable, improving, rapidly worsening, or slowly worsening) there is no one single defining biomedical parameter or cutoff, HFP may play a role in suggesting cutoffs and/or reference values for individual or combinations of parameters, thus allowing to further increase the efficacy of the monitoring service of the HFP.

8.1.3 Prognosis in Chronic Heart Failure.

Defining prognosis in HF is complex for the reasons outlined in section 6.

From the operational standpoint, for the prognostic evaluation the following HF features will be taken into account:

a. diagnosis of HF
b. evolutionary stage (stable, improving, slowly or rapidly worsening)
c. severity class (NYHA, clinical profiles in acutely decompensated, other).

a. Diagnosis of HF. The imprecision in making the diagnosis of HF does not help in defining the prognosis of this syndrome. In fact, information on prognosis available in HF guidelines mostly pertains to HF with reduced ejection fraction whereas limited prognostic information is available for HF with preserved left ventricular function (the prevalent type in elderly subjects).

b. Evolutionary stage. In particular, patients conditions will be considered separately as the prognostic stratification allowed by parameters chosen among demographis/historical, clinical, electrophysiologic, functional, and echocardiographic ones (see Table-3, section 6)

- during a stable HF it has a long-term aim which is to predict, and hopefully prevent, acute decompensation, hospital admission and death in the mid-term and long-term, whereas
- during an acutely decompensated HF has a short-term aim which is to guide immediate treatment decisions.

c. Severity class. Severity classes will be considered separately, as the prognostic value of a number of parameters changes from early to advanced heart failure.

Potential contributions of the HFP in defining HF prognosis in Workflow 1.

Problem statement 10.
As the predictive value of a parameters may change from HF with reduced or preserved EF, HFP may help in the difficult task of identifying the single biomedical parameter or the combination of parameters, with relative cutoffs, with predicting value in each of these main diagnostic classes of HF.

Problem statement 11.
Monitoring performed by HFP might allow to identifying the single biomedical parameter or the combination of parameters (among demographics/historical, clinical, electrophysiologic, functional, and echocardiographic ones) with relative cutoffs, with predicting value in each of the conditions among stable, improving, rapidly or slowly worsening.

Problem statement 12.
As the predictive value of a parameters may change from early to advanced heart failure, HFP may help in identifying the single biomedical parameter or the combination of parameters, with relative cutoffs, with predicting value in each severity class of HF.

Additionally, HFP may help in verifying if the Clinical classification of acutely decompensated HF adds prognostic value to the NYHA classification.

Problem statement 13.
On large scale, in the future, by collecting, integrating, and processing biomedical data, the HFP will allow on large random patient samples (followed for an adequate period), to determine the prognostic weight of numerous and unselected variables undergoing sequential determination (chosen among demographics and historical, clinical, electrophysiologic, functional, and echocardiographic and other parameters).

Additionally, it may allow to determine whether guidelines improve the quality of clinical practice and the utilization of health resources.

8.2 Problem Statement and formulation of the Decision Making Problems relevant to Workflow 2.

In Fig 4. HFP level 1, 2 and 3 and patient n. 2.

For the processes of diagnosis, management, prognosis assessment, the same rules, actions, and problem statements listed in workflow 1 do apply

During the management and prognosis phase home devices (controlled by HFP level 3) providing reminders on pharmacological and non-pharmacological measures may improve compliance to treatment and hence outcome.

Additionally, several biomedical parameters, relevant symptoms and compliance to prescribed pharmacological and non pharmacological regimens will be **telemonitored** by HFP level 3 in patients' homes.

UNICZ, UNIMIB and AUXOL suggested to telemonitor some parameters in order to achieve an early diagnosis of decompensation, i.e. before it is clinically manifest. Earlier detection of patient's decompensation permits a better optimization of the therapy, a better outcome and a reduction of the health costs. Selected variations of telemonitored parameters of interest include:

8.2.1 Reduction of systolic blood pressure

Ventricular systolic dysfunction is characterized by a loss of contractile strength of the myocardium, which initially is compensated by ventricular hypertrophy and/or dilation and neurohormonal mechanisms. When, however, compensatory mechanisms are no longer able to maintain cardiac output, a decrease in systolic blood pressure is seen.

8.2.2 Increase of heart rate vs basal value.

Applicable only to patients in sinus rhythm in whom the heart rate should be measured over one minute, in the supine position, at least two times.
In patients with HF the activation of the sympathetic nervous system and, thus, hyperadrenergic state related mainly to changes if body fluid status may cause tachycardia and arrhythmias. Therefore, an increase in heart rate as a simple marker of autonomic regulation may predict HF worsening.

8.2.3 Increase of the respiratory rate and width of chest movements.

Due to a number of pathophysiological changes, HF worsening can thus result in exertional dyspnea (shortness of breath during exertion) or dyspnea at rest, with the respiratory movements becoming more frequent and superficial

8.2.4 Increase % of body water.

Bioimpedance permits an easy and fairly accurate assessment of changes in body fluid content and may be useful in predicting potentially harmful fluid overload.
In HF, there is a compensatory increase in blood volume that serves to increase ventricular preload and thereby enhance systolic output. However, the increase of hydrostatic intravascular pressure facilitates the exit of fluid in the extravascular compartment, which, at the end, can lead to pulmonary and systemic oedema.

Less accurate indices of fluid status in patients with HF include kilograms of body weight and volume of urinary daily output.

8.2.5 Variation of body temperature.

In order to compensate for reduced cardiac output during HF, feedback mechanisms within the body try to maintain normal arterial pressure by constricting arterial resistance vessels through activation of the sympathetic adrenergic nervous system, thereby increasing systemic vascular resistance. This could be responsible for modification of body temperature when the haemodynamic situation changes.

Potential contributions of the HFP in the management of chronic heart failure in Workflow 2

Problem statement 14.
By the adjunct of HFP level 3, capable of engaging with the patients by providing informative material, reminders on medications' and measurements' schedule, the HFP is expected to improve the compliance to the prescribed regimen (as compared to compliance in Workflow 1).

Problem statement 15.
The adjunct of HF level 3, allowing the repeated home telemonitoring of relevant symptoms and of biomedical parameters like blood pressure, heart rate, respiratory frequency and movements width, % of body water, weight, urinary output and body temperature, is expected to further improve some crucial aspects of HF management as compared to Workflow 1.

In particular, home telemonitoring is expected to:
Improve classification of HF symptoms' severity,
perform closer monitoring and earlier most appropriate management change,
identify earlier potential precipitating and exacerbating factors of decompensated CHF.

Problem statement 16. The adjunct of HF level 3, is expected to further improve some crucial aspects of HF prognosis assessment as compared to Workflow 1.

8.3 Problem Statement and formulation of the Decision Making Problems relevant to Workflow 3.

In workflow 3, while supporting the standard CHF management and prognosis assessment, the adjunct of level 4 of HFP will assist in collecting biomedical information for research and development purposes.

Newly validated parameters and more integrated approaches may offer, in the future, improved diagnostic accuracy and more robust prognostic algorithms for in heart failure.

For example, new prognostic markers and risk (or protecting) factors might thus originate from:

- continuous non invasive heart rate and beat-by-beat blood pressure measurements;
- cardiopulmonary stress test (with breath-by-breath measurement of O^2 consumption and CO^2 production and the calculation functional parameters like peak O^2 consumption and the slope of minute ventilation / CO^2 production);
- genomics and proteomics
- new laboratory tests
- …… *(endless list)*

8.3.1 New potential prognostic factors.

8.3.1.a Parameters of autonomic cardiac dysregulation.

In chronic heart failure irrespective of its aetiology complex changes in autonomic function are characteristically present. An increase in sympathetic outflow to the heart and to the peripheral vasculature and a reduction in cardiac vagal outflow to the heart have been described.

Heart rate variability (HRV), blood pressure variability (BPV) and baroreflex sensitivity (BRS) are useful tools for the assessment of autonomic cardiovascular regulation. Certain patterns of autonomic cardiovascular regulation have been proven to have prognostic value.

a1- Decreased heart rate variability (HRV). HRV provides physiologically and prognostically important information on the autonomic control of heart period in heart failure. A number of studies have shown that decreased HRV is related to a higher risk of mortality in patients with HF. In addition, the positive effect of exercise training in HF involves an attenuation of the reduced HRV response, and this improvement may have prognostic significance.
The clinical value of HRV in HF management needs to be determined.

a2- Decreased blood pressure variability (BPV). Blood pressure fluctuations appear to be affected mostly by sympathetic activity. Decreased BPV in patients with HF could be related to left ventricular dysfunction and thus increase the risk of adverse events. It remains to be verified if BPV measures may improve the therapeutic strategy in HF patients.

a3- Decreased baroreflex sensitivity (BRS). BRS provides a measure of the gain of the reflex arc which modulates changes in heart period in response to changes in blood pressure. In general, impaired BRS is associated with reduced cardiac

vagal control and with increased sympathetic efferent activity. An impairment of baroreflex control of HR is an early predictor of autonomic dysfunction in several conditions and may have independent prognostic relevance in patients with cardiovascular diseases. Its usefulness in HF management is, however, still largely unknown, although evidence is available that a reduced sensitivity of baroreflex control of heart rate carries an adverse prognosis.

8.3.1.b Parameters of decreased exercise capacity.

A decreased exercise capacity is an overall indicator or cardiovascular compromise. Exercise duration, peak VO_2, high VE/VCO_2 slope, have proven to have prognostic value. The latter, in particular, is a rather comprehensive measure.

Additional parameters measurable in a cardiopulmonary stress test include: workload, blood pressure, heart rate, peak VCO2, anaerobic threshold, O2 pulse, respiratory quotient.

Problem statement 17. The adjunct of HF level 4, is expected to further improve some crucial aspects of HF prognosis assessment as compared to Workflow 1 by validating available sophisticated markers and by identifying new ones.

Problem statement 18. Genetic, genomic and proteomic technologies aiming at developing new pathogenetic, prognostic and therapeutic aspects of heart failure, typically generate large amounts of data which must be analyzed by the most appropriate statistical techniques. The HFP may help the bioinformatics to handle and to make sense of large quantities of data.

9 Conclusions

In conclusion, the deliverable number five *"Medical – clinical processes and requirements in HF domain. Relevance to formulation of the decision making problems",* collecting the results of the tasks T1.1 and T1.2 of the Work Package WP1, prepared by UNICAL, UNICZ, JUMC, UNIMIB and AUXOL, intended to give a general overview of both the heart failure medical domain and of the general architecture of the technological HEARFAID platform tailored on such domain.

In particular, main services and functions of the HEARFAID platform have been articulated based on the typical workflows followed by subjects with either suspected or proven heart failure. Such services are seen as a support to patients with CHF and to the medical personnel involved in their management, as well as to patients' relatives involved in their care, all of them acting in their respective environments.

Additionally, while assisting both the medical personnel and the patients in relation to key aspects of standard diagnosis, management, and prognosis assessment (fully adhering to the European Society of Cardiology Guidelines for congestive heart failure management), the HFP might be able to collect, integrate and elaborate data in order to generate new knowledge in the field of heart failure. A number of open questions still exist in the field of HF. The outline of the problem statements clearly shows that the HFP might in the future contribute substantially to find an answer to most of them.

Finally, by improving the implementation of the Guidelines by both the medical personnel and the patients (followed also at home), the HFP might ultimately help in decreasing the rate of morbidity and mortality and the health care costs pertaining to heart failure.

Annex 1: List of biomedical signs and symptoms.

1. Medical history:

- Cardiovascular history:

  angina, atrial fibrillation/flutter, ventricular arrhythmias, hypertension, myocardial infarction, peripheral vascular disease, coronary artery revascularization, valvular heart disease, thromboendatherectomy, cerebrovascular events (stroke, TIA)
- Cardiac resynchronization therapy
- Implantable cardioverter-defibrillator
- Endocrine/metabolic: diabetes (type 1 or 2), hyper/hypothyroidism, obesity, metabolic syndrome
- Renal: impaired renal function
- Hematological: anemia
- Respiratory: chronic obstructive heart lung disease
- Gastrointestinal: ulcerative colitis, Crohn disease, gastritis, peptic ulcer, GERD
- Hepatic: hepatitis, jaundice, cirrhosis
- Psychiatric
- Neurological: degenerative disorders
- Current treatment: beta blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, oral anticoagulants, heparine, antiarrhythmics, antiplatelet drugs, digoxin

2. Symptoms

- Fatigue
- Breathlessness
- NYHA class (I-IV)
- Orthopnea
- Nocturnal dyspnea
- Weight change
- Peripheral oedema (monolateral, bilateral)

3. Signs

- Sitting blood pressure and heart rate
- Respiratory rate
- Third or fourth heart sound
- Pulmonary crepitations
- Jugular vein congestion
- Liver enlargement

Annex 2: List of parameters of selected tests.

1. Electrocardiogram

- heart rhythm: sinus / arrhythmia (atrial fibrillation/flutter)
- heart rate
- conduction: PR, QRS, QT, LBBB, RBBB
- morphology (pathological Q waves)
- ST depression (mm)
- left ventricular hypertrophy (Sokolow-Lyon - S1-2 + R5-6)

2. Holter electrocardiography

- Heart rate: mean, minimum, maximum (24h, daytime, nighttime)
- Ventricular ectopic beats/24h
- Supraentricular ectopic beats /24h
- Other arrhythmias
- Conduction abnormalities
- Heart rate variability

3.Chest X-ray: PA and side view

- Cardio-thoracic ratio
- pulmonary congestion / oedema

4. Clinical chemistry

- Complete blood count (Hb, red blood count, leukocytes, platelet count)
- Electrolytes (sodium, potassium, chloride)
- Bicarbonate
- creatine kinase
- lipids (TC, LDL-C, HDL-C, TG)
- creatinine
- glucose
- AST, ALT
- Uric acid
- Urea
- TSH

- Creatinine clearance (Cockroft and Gault Formula)
- Glycated Hb in diabetic patients
- BNP
- C-reactive protein
- Fibrinogen

5. Echocardiography

Left ventricle

- end-diastolic diameter
- end-systolic diameter
- interventricular septum diastolic thickness
- posterior wall diastolic thickness
- end-diastolic volume
- end-systolic volume
- ejection fraction (Simpson's) (2D, 4D)

Right ventricle

- end-diastolic diameter
- TAPSE

Left atrium

- Anteroposterior diameter

Aorta

- Root diameter
- Ascending aorta diameter

Mitral valve

- Emax/Amax
- Deceleration time
- Mitral regurgitation (EROA, Doppler shift)

Tricuspid valve

- Pulmonary artery pressure (Tricuspidal regurgitation)

6. 6-minute walking test

- walking distance
- BP, HR, SpO2 (baseline and end)

17. Quality of life:

- Minnesota Living with Heart Failure score
- SF 36 score

Annex 3: List of parameters relevant for prognosis

1) **Heart rate**
   - change in clinic heart rate.
   - change in heart rate in Holter ECG monitoring
2) **Respiratory rate**
   - change in respiratory rate
3) **Temperature**
   - change in body temperature
4) **Blood pressure**
   - change in systolic and diastolic BP
5) **Clinical Chemistry**
   - BNP level
   - Hematocrit
   - Plasma sodium level
   - Serum creatinin level
   - Serum bilirubin level
6) **Echocardiography: changes in**
   - Ejection fraction
   - Diastolic diameter of left ventricle
   - Pulmonary artery pressure
   - mitral regurgitation (Doppler grading, Eroa)
   - Diastolic function (E/A, Deceleration time
   - TAPSE
7) **Potential new prognostic markers:**
   - Arterial tonometry and waveform analysis
   - Home blood pressure measurement
   - 24 h ambulatory blood pressure monitoring (Spacelabs 90207)
   - Endothelial function (endothelin, NO, strain-gauge plethysmography flow-mediated vasodilation, forearm i.a. drug infusion)
   - Autonomic parameters (heart rate variability, blood pressure variability, baroreflex sensitivity) (Finometer device)

- Bioimpedance – estimation of changes in body water content.

8) Cardiopulmonary stress testing (instead of 6 min walking test in some patients)

Main prognostic markers:

- Exercise duration
- Peak VO_2
- VE/VCO_2 slope

Additional parameters:

- Workload
- Blood pressure
- Heart rate
- Peak VCO_2
- Anaerobic threshold
- O_2 pulse
- VE/VO_2
- Respiratory quotient